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(54) Title: METHODS FOR TREATING VIRAL INFECTIONS

(57) Abstract

The present invention relates to methods of treating a vertebrate, particularly a mammal and more particularly murine or human patient, suffering from one or more viral infections, or a cell line infected with one or more viral infections, said viral infections including but not limited to the infections of the following viruses: hepatitis C, HIV, hepatitis A, hepatitis B, hepatitis G, or hepatitis H, by administering to said patient infected with at least one of virus at least one statin or statin-like compound determined to have anti-viral activity according to the present invention, said anti-viral statin or statin-like compound being selected from the group consisting of: mevastatin, lovastatin, pravastatin, simvastatin, and the compounds disclosed in U.S. Patents Nos. 4,346,227, 4,448,979, 4,739,073, 5,273,995, 5,169,857, 5,006,530, and 5,401,746.

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METHODS FOR TREATING VIRAL INFECTIONS

Field of the Invention

The present invention relates to the field of medicine generally, and particularly relates to the treatment of viral infections, and more particularly relates to the use of statin compounds such as mevastatin and other statin-like compounds in the treatment of viral infections.

Background of the Invention

Compounds designated mevastatin, lovastatin, pravastatin (as disclosed in U.S. Patent No. 4,346,227) and simvastatin are known and are known to inhibit the activity of HMG-CoA reductase, and to limit cholesterol biosynthesis (as disclosed in U.S. Patent No. 5,376,383).

For example, U.S. Patents Nos. 4,346,227 and 4,448,979 disclose that certain members of the disclosed class of compounds (a class that includes pravastatin) are capable of inhibiting biosynthesis of cholesterol and are thus useful in the treatment of hypercholesteraemia.

U.S. Patent No. 4,739,073 discloses that certain members of the class of compounds defined therein may be used to inhibit cholesterol blosynthesis and to lower the blood cholesterol level and, therefore, are useful in the treatment of hyperlipoproteinemia and atherosclerosis.

U.S. Patent No. 5,273,995 discloses that compounds defined therein provide surprising inhibition of the biosynthesis of cholesterol, and may be used to treat mammals, including humans, suffering from hypercholesterolemia, or may be useful as hypolipidemic or hypocholesterolemic agents.

U.S. Patents Nos. 5.169,857, 5,006,530 and 5,401,746 disclose that certain members of the class of compounds described therein are useful in treating hyperproteinaemia, lipoproteinaemia, and arteriosclerosis, and exhibit inhibitory action on HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl coenzyme A reductase) and are consequently inhibitors of cholesterol biosynthesis, and additionally cause a lowering of cholesterol content in the blood.

U.S. Patent No. 5,006,530 discloses that certain members of the class of compounds described therein are useful in treating circulatory diseases.

Summary of the Invention

In accordance with the present invention, it has been surprisingly and unexpectedly found that certain compounds known in the art, including but not limited to mevastatin, lovastatin, pravastatin and sirnvastatin, are effective in treating a vertebrate, particularly a mammal and more particularly murine or human patient, suffering from one or more viral infections viral infection, treating viral infection, such viral infections include but are not

limited to HIV, or hepatitis, including but not limited to hepatitis C, hepatitis A, hepatitis B, hepatitis G, and hepatitis H.

The present invention relates to methods of treating viral infection by administering to patients suffering from one or more viral infection at least one compound selected from the group consisting of mevastatin, lovastatin, pravastatin and simvastatin, and all analogues, metabolites, and precursors thereof, and all physiologically acceptable salts and pro-drug esters thereof.

Furthermore, in accordance with the present invention, it has been found that, surprisingly and unexpectedly, the compounds disclosed in U.S. Patents Nos. 4,346,227, 4,448,979, 4,739,073, 5,273,995, 5,169,857, 5,006,530, and 5,401,746 as being useful in the treatments disclosed therein are effective in treating viral infection, such viral infections include but are not limited to HIV, or hepatitis, including but not limited to hepatitis C, hepatitis A, hepatitis B, hepatitis G, and hepatitis H.

The present invention relates to methods of treating a vertebrate afflicted with a viral infection by administering to said vertebrate suffering from one or more viral infection at least one compound (or physiologically acceptable salt or pro-drug ester thereof) selected from the groups of compounds (and all analogues, metabolites, precursors thereof) disclosed in any of the follow U.S. patents: U.S. Patents Nos. 4,346,227, 4,448,979, 4,739,073, 5,273,995, 5,169,857, 5,006,530, and 5,401,746 as being useful in the treatments described in any of those patents, other than the treatment of viral infection.

Neither any known single prior art reference nor the patents cited herein, either alone or in combination, contain a disclosure which would give rise to any expectation, in an ordinarily skilled artisan, that the antiviral statin and statin-like compounds, according to the present invention, would be useful, to any degree, in the treatment of a vertebrate having a viral infection. Nor does the prior art provide a motivation to those of skill in the art to try any of the statin or statin-like compounds according to the present invention in a treatment of any vertebrate having or suffering from a viral infection.

Detailed Description of the Preferred Embodiment of the Present Invention

The present invention relates to methods of treating viral infection by administering to patients suffering from one or more viral infection at least one of the compounds according to the present invention.

The term "pro-drug ester," as used herein, especially when referring to a pro-drug ester of the anti-viral statin and statin-like compounds, refers to a chemical derivative of the compound that is rapidly transformed *in vivo* to yield the compound, for example, by hydrolysis in blood. The term "pro-drug ester" refers to derivatives of the compound of the present invention formed by the addition of any of several ester-forming groups that are hydrolyzed under physiological conditions. Examples of pro-drug ester groups include

pivoyloxymethyl, acetoxymethyl, phthalidyl, indanyl and methoxymethyl, as well as other such groups known in the art, including a (5-R-2-oxo-1,3-dioxolen-4-yl)methyl group. Other examples of pro-drug ester groups can be found in, for example, T. Higuchi and V. Stella, in "Pro-drugs as Novel Delivery Systems", Vol. 14, A.C.S. Symposium Series, American Chemical Society (1975); and "Bioreversible Carriers in Drug Design: Theory and Application", edited by E. B. Roche, Pergamon Press: New York, 14-21 (1987) (providing examples of esters useful as prodrugs for compounds containing carboxyl groups).

The term "pharmaceutically acceptable salt," as used herein, especially when referring to a pharmaceutically acceptable salt of the anti-viral statin and statin-like compounds, refers to any pharmaceutically acceptable salts of a compound, and preferably refers to an acid addition salt of a compound. Preferred examples of pharmaceutically acceptable salt are the alkali metal salts (sodium or potassium), the alkaline earth metal salts (calcium or magnesium), or ammonium salts derived from ammonia or from pharmaceutically acceptable organic amines, for example C_1-C_7 alkylamine, cyclohexylamine, triethanolamine, ethylenediamine or tris-(hydroxymethyl)-aminomethane. With respect to compounds of the invention that are basic amines, the preferred examples of pharmaceutically acceptable salts are acid addition salts of pharmaceutically acceptable inorganic or organic acids, for example, hydrohalic, sulfuric, phosphoric acid or aliphatic or aromatic carboxylic or sulfonic acid, for example acetic, succinic, lactic, malic, tartaric, citric, ascorbic, nicotinic, methanesulfonic, p-toluensulfonic or naphthalenesulfonic acid.

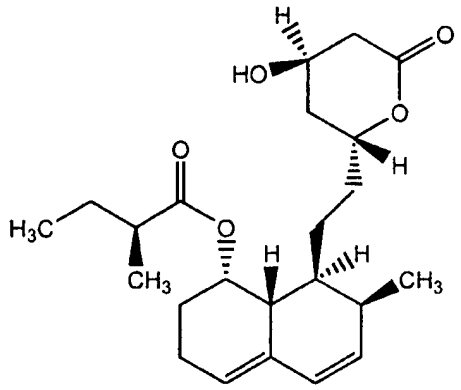
Preferred pharmaceutical compositions of the present invention include pharmaceutically acceptable salts and pro-drug esters of the anti-viral statin and statin-like compounds disclosed herein. Accordingly, if the manufacture of pharmaceutical formulations involves intimate mixing of the pharmaceutical excipients and the active ingredient in its salt form, then it is preferred to use pharmaceutical excipients which are non-basic, that is, either acidic or neutral excipients.

The expression "antiviral statin and statin-like compounds", as herein, refers to the group of compounds (including any possible stereoisomers in any ratios, including isolated or substantially isolated stereoisomers) consisting of mevastatin, lovastatin, pravastatin and simvastatin, and therein derivatives, compounds disclosed in any of U.S. Patents Nos. 4,346,227, 4,448,979, 4,739,073, 5,273,995, 5,169,857, 5,006,530, and 5,401,746 as being useful in the particular treatments described in any of those patents, and all analogues, metabolites and precursors of mevastatin, lovastatin, pravastatin, simvastatin and the compounds disclosed in U.S. Patents Nos. 4,346,227, 4,448,979, 4,739,073, 5,273,995, 5,169,857, 5,006,530, and 5,401,746, as mentioned above, and all physiologically acceptable salts and pro-drug esters thereof.

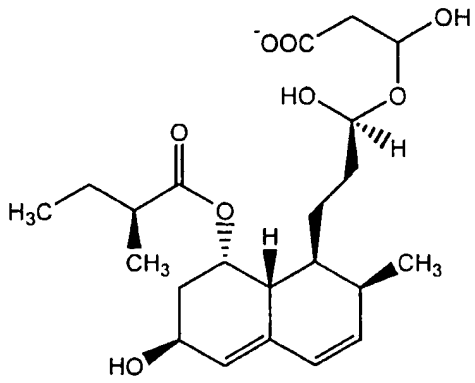
The entireties of U.S. Patents Nos. 4,346,227, 4,448,979, 4,739,073, 5,273,995, 5,169,857, 5,006,530, and 5,401,746, and all other patent documents and other publicly available documents are hereby incorporated by reference herein, and with particularity, are incorporated herein with regard to their disclosure of the anti-viral statin and statin-like compounds disclosed and with regard to their disclosure of the particular treatments, amount, and modes of treatment of those compounds with regard to the particular condition or malady for which they are shown of suggested to be useful.

The following are non-limiting examples of specific compound or classes of compounds that are within the definition of "antiviral statin and statin-like compounds," as that and related terms are used herein.

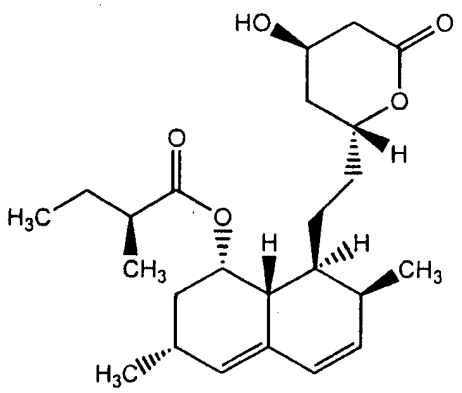
Mevastatin ([1S-[1 alpha (R*), 7 beta (2S*,4S*),5A beta]]-2- methylbutanoic acid 1,2,3,7,8,8A-hexahydro-7-methyl-8-[2-tetrahydro-4- hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester) has the formula:



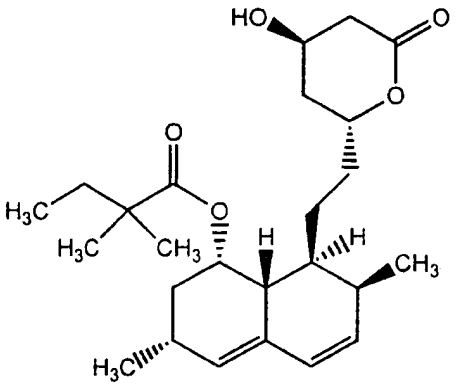
Pravastatin ([1S-[1 alpha (beta S*, delta S*), 2 alpha 6 alpha 8 beta - (R*), 8 alpha)]1,2,6,7,8,8A-hexahydro-beta, delta, 6-trihydroxy-2-methyl-8- (2-methyl-1-oxo butoxy)-1-naphthaleneheptanoic acid) has the formula



Lovastatin ([1 S-[1 alpha (R*), 3 alpha, 7 beta, 8 beta (2S*,4S*),-8A beta)]-2-Methylbutanoicacid1,2,3,7,8,8A-hexahydro-3,7-dimethyl-8-[2-(tetrahydro -4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester) has the formula:

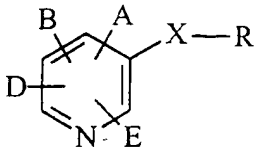


Simvastatin ([1S-[1 alpha, 3 alpha, 7 beta, 8 beta (2S*,4S')-8A beta]]-2,-2-dimethylbutanoic acid 1,2,3,7,8,8A-hexahydro-3,7,-dimethyl- 8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester) has the formula:



These compounds may be synthesized or isolated from natural sources according to methods and techniques well known in the art.

The anti-viral statin or statin-like compounds disclosed in U.S. Patent Nos. 5,401,746, 5,169,857, and 5,006,530 include substituted pyridines having the following general structures:



wherein A-- stands for heteroaryl which can be monosubstituted, disubstituted or trisubstituted by identical or different halogen, alkyl, alkoxy, alkylthio, alkylsulphonyl, aryl, aryloxy, arylthio, arylsulphonyl, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, alkoxycarbonyl or by a group of the formula --N R^1 R^2,

wherein

R^1 and R^2 -- are identical or different and denote alkyl, aryl, aralkyl, acyl, alkylsulphonyl or arylsulphonyl, or stands for aryl which can be mono-substituted to penta-substituted by identical or different alkyl groups which can be optionally substituted by hydroxyl or alkoxy, by alkoxy, alkylthio, alkylsulphonyl, aryl, aryloxy, arylthio, arylsulphonyl, aralkyl, aralkoxy, aralkylthio, aralkylsulphonyl, halogen, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, alkoxycarbonyl, sulphamoyl, dialkylsulphamoyl, carbamoyl, dialkylcarbamoyl or by a group of the formula --N R^1 R^2,

wherein

R^1 and R^2 have the abovementioned meaning and denote straight chain or branched alkyl,

B -- stands for cycloalkyl, or stands for alkyl which can be substituted by halogen, cyano, alkoxy, alkylthio, alkylsulphonyl, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphonyl, alkoxycarbonyl, acyl or by a group of the formula --N R^1 and R^2,

wherein

R^1 and R^2 --are identical or different and denote alkyl, aryl, aralkyl, acyl, alkylsulphonyl or arylsulphonyl, or by carbamoyl, dialkyl carbamoyl, sulphamoyl, dialkylsulphamoyl, heteroaryl, aryl, aryloxy, arylthio, arylsulphonyl, aralkoxy, aralkylthio or aralkylsulphonyl, where the heteroaryl and aryl radicals of the last mentioned substituents can be mono substituted, disubstituted or trisubstituted by different halogen, cyano, trifluoromethyl, trifluoromethoxy, alkyl, alkoxy, alkylthio or alkylsulphonyl,

D and E are identical or different and stand for hydrogen, or stand for CN or NO_2, or stand for cycloalkyl, or stand for straight-chain or branched alkyl which can be substituted by azido, halogen, hydroxy, cyano, alkoxy, alkylthio, alkylsulphonyl, trifluoromethyl,

trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphonyl, alkoxycarbonyl, acyl or by a group of the formula --N R^1 R^2, wherein R^1 and R^2 have the abovementioned meaning, or by carbamoyl, dialkylcarbamoyl, sulphamoyl, dialkylsulphamoyl, heteroaryl, aryl, aryloxy, arylthio, arylsulphonyl, aralkoxy, aralkylthio or aralkylsulphonyl, where the heteroaryl and aryl radicals can be monosubstituted, disubstituted or trisubstituted by identical or different halogen, cyano, trifluoromethyl, trifluoromethoxy, alkyl, alkoxy, alkylthio or alkylsulphonyl, or stand for heteroaryl which can be monosubstituted, disubstituted or trisubstituted by identical or different halogen, alkyl, alkoxy, alkylthio, alkylsulphonyl, aryl, aryloxy, arylthio, arylsulphonyl, trifluoromethyl, trifluoromethoxy, trifluoromethylthio or alkoxycarbonyl, or by a group of the formula --N R^1 R^2,

wherein R^1 and R^2 have the abovementioned meaning, or stand for aryl which can be monosubstituted to pentasubstituted by identical or different alkyl which can be optionally substituted by hydroxyl or alkoxy, by alkoxy, alkylthio, alkylsulphonyl, aryl, aryloxy, arylthio, arylsulphonyl, aralkyl, aralkoxy, aralkylthio, aralkylsulphonyl, halogen, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, alkoxycarbonyl, sulphamoyl, dialkylsulphamoyl, carbamoyl or dialkylcarbamoyl, or by a group of the formula --N R^1 R^2, wherein R^1 and R^2 have the abovementioned meaning, or stand for a group of the formula --N^3 R^4, --COR^5 or --CR^{11} R^{12} --Y, wherein R^3 and $R^4$are identical or different and denote hydrogen or denote alkyl, aryl or aralkyl, or denote a group of the formula --COR^6 or --SO_2 R^7, or and R^3 and R^4 together form an alkylidene chain which can be interrupted by N, O, S and/or N-alkyl, N-aryl, N-aryl, N-carbamoyl or N-alkoxycarbonyl,

R^6 stands for hydrogen, or stands for a group --NHR^8, or stands for alkoxy, or stands for alkyl, aryl, aryloxy, aralkyl, aralkoxy or heteroaryl, where the radicals mentioned can be monosubstituted, disubstituted or trisubstituted by identical or different alkyl, alkoxy, alkylthio, halogen, cyano, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, amino, alkylamino or dialkylamino, R^7--stands for cycloalkyl, or stands for alkyl which can be substituted by cyano, halogen, trifluoromethyl, trifluoromethoxy or alkoxycarbonyl, or stands for aryl, aralkyl or heteroaryl, where the radicals mentioned can be monosubstituted, disubstituted or trisubstituted by identical or different alkyl, alkoxy, alkylthio, halogen, cyano, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, amino, alkylamino or dialkylamino, and R^8--stands for hydrogen, or stands for cycloalkyl, or stands for alkyl which is optionally substituted by cyano, halogen, trifluoromethyl or trifluoromethoxy or stands for aryl, aralkyl or heteroaryl, where the radicals mentioned can be monosubstituted, disubstituted or trisubstituted by identical or different alkyl, alkoxy, alkylthio, halogen, cyano, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, amino, alkylamino or dialkylamino,

R^5 --denotes hydrogen, cycloalkyl, hydroxyl, alkoxy, trimethylsilylalkoxy, aryloxy or aralkoxy, or stands for a group of the formula --N R^9R^{10},

wherein R^9 and R^{10} are identical or different and denote hydrogen, alkyl, aryl or aralkyl, or denote an optionally substituted heterocyclic radical, which is bonded via a nitrogen atom, from the series comprising pyrrolidine, piperidine, morpholine, thiomorpholine or piperazine, and R^{11} and R^{12}can be identical or different and stand for hydrogen, or stand for alkyl which can optionally be substituted by hydroxyl, halogen, alkoxy or alkoxycarbonyl, or stand for cycloalkyl, or

R^{11} and R^{12} together form a saturated or unsaturated carbocyclic or heterocyclic ring having up to 6 carbon atoms, and

Y--denotes a group of the formula --NR $R^{13}R^{14}$, --COR^{15}, --S--R^{16}, --SO--R^{16}, --SO_2R^{16}, --OR^{17}or $-N_3$, wherein R^{13} and $R^{14}$are identical or different and stand for hydrogen, alkyl, aryl or aralkyl, where the aryl radicals can be substituted by halogen, cyano, alkyl, alkoxy or trifluoromethyl, or stand for a group of the formula --COR^{15} or --SO_2R^{16}, or

R13 and R14 together form an alkylene chain which can be interrupted by N, O, S and/or N-alkyl, N-aryl, N-aralkyl, N-carbamoyl or N-alkoxycarbonyl,

R15 --denotes hydrogen, or denotes a group --NR18 R19, or denotes alkyl or alkoxy, or denotes aryl, aryloxy, aralkyl, aralkoxy or heteroaryl, where the radicals mentioned can be monosubstituted, disubstituted or trisubstituted by identical or different alkyl, alkoxy, alkylthio, halogen, cyano, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, amino, alkylamino or dialkylamino,

R16 --denotes cycloalkyl, or denotes straight-chain or branched alkyl which can be substituted by cyano, halogen, trifluoromethyl, trifluoromethoxy or alkoxycarbonyl, or

denotes aryl, aralkyl or heteroaryl, where the radicals mentioned can be monosubstituted, disubstituted or trisubstituted by identical or different alkyl, alkoxy, alkylthio, halogen, cyano, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, amino, alkylamino or dialkylamino, or denotes trimethylsilyl or dimethylethylsilyl, or denotes a group --NR9 R10, where R9 and R10 have the abovementioned meaning,

R17 --stands for hydrogen, or stands for cycloalkyl, or stands for alkyl which can be substituted by halogen, cyano, alkoxy, alkylthio, alkylsulphonyl, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphonyl, alkoxycarbonyl or acyl, or by a group of the formula --NR1 R2, wherein

R1 and R2 have the abovementioned meaning, or by carbamoyl, dialkylcarbamoyl, sulphamoyl, dialkylsulphamoyl, heteroaryl, aryl, aryloxy, arylthio, arylsulphonyl, aralkoxy, aralkylthio or aralkylsulphonyl, where the heteroaryl and aryl radicals can be monosubstituted, disubstituted or trisubstituted by identical or different halogen, cyano, trifluoromethyl, trifluoromethoxy, alkyl, alkoxy, alkylthio or alkylsulphonyl, or stands for

heteroaryl which can be monosubstituted, disubstituted or trisubstituted by identical or different halogen, alkyl, alkoxy, alkylthio, alkylsulphonyl, aryl, aryloxy, arylthio, arylsulphonyl, trifluoromethyl, trifluoromethoxy, trifluoromethylthio or alkoxycarbonyl, or by a group of the formula --NR^1R2,

wherein

R1 and R2 have the abovementioned meaning, or stands for aryl which can be monosubstituted to pentasubstituted by identical or different alkyl, alkoxy, alkylthio, alkylsulphonyl, aryl, aryloxy, arylthio, arylsulphonyl, aralkyl, aralkoxy, aralkylthio, aralkylsulphonyl, halogen, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, alkoxycarbonyl, sulphamoyl, dialkylsulphamoyl, carbamoyl or dialkylcarbamoyl, or by a group of the formula --NR1 R2,

wherein

R1 and R2 have the abovementioned meaning, or stands for 2,5-dioxo-tetrahydropyrryl, stands for tetrahydropyranyl, or stands for trialkylsilyl , or denotes a group COR16,

where R16 has the abovementioned meaning, and R18 and R19 are identical or different and denote hydrogen, or denote cycloalkyl, or denote alkyl which is optionally substituted by cyano, halogen, trifluoromethyl or trifluoromethoxy, or denote aryl, aralkyl or heteroaryl, where the radicals mentioned can be monosubstituted, disubstituted or trisubstituted by identical or different alkyl, alkoxy, alkylthio, halogen, cyano, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, amino, alkylamino or dialkylamino, or D and E together stand for an organic radical.

These compounds may be synthesized or isolated from natural sources according to methods and techniques well known in the art.

In the context of the above-described substituted pyridines, cycloalkyl in general stands for a cyclic hydrocarbon radical having 3 to 8 carbon atoms. The cyclopropyl, cyclopentyl and cyclohexyl ring is preferred. Examples which may be mentioned are cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

In the context of the above-described substituted pyridines, alkyl in general stands for a straight-chain or branched hydrocarbon radical having 1 to 12 carbon atoms. Lower alkyl having 1 to about 6 carbon atoms is preferred. Examples which may be mentioned are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl, hexyl, isohexyl, heptyl, isoheptyl, octyl and isooctyl.

In the context of the above-described substituted pyridines, alkoxy in general stands for a straight-chain or branched hydrocarbon radical having 1 to 12 carbon atoms which is bonded via an oxygen atom. Lower alkoxy having 1 to about 6 carbon atoms is preferred. An alkoxy radical having 1 to 4 carbon atoms is particularly preferred. Examples

which may be mentioned are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentoxy, isopentoxy, hexoxy, isohexyloxy, heptoxy, isoheptoxy, octoxy and isooctoxy.

In the context of the above-described substituted pyridines, alkylthio in general stands for a straight-chain or branched hydrocarbon radical having 1 to 12 carbon atoms which is bonded via a sulphur atom. Lower alkylthio having 1 to about 6 carbon atoms is preferred. An alkylthio radical having 1 to 4 carbon atoms is particularly preferred. Examples which may be mentioned are methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, pentylthio, isopentylthio, hexylthio, isohexylthio, heptylthio, isoheptylthio, octylthio, and isooctylthio.

In the context of the above-described substituted pyridines, alkylsulphonyl in general stands for a straight-chain or branched hydrocarbon radical having 1 to 12 carbon atoms which is bonded via an SO_2 group. Lower alkylsulphonyl having 1 to about 6 carbon atoms is preferred. Examples which may be mentioned are: methylsulphonyl, ethylsulphonyl, propylsulphonyl, isopropylsulphonyl, butylsulphonyl, isobutylsulphonyl, pentylsulphonyl, isopentylsulphonyl, hexylsulphonyl and isohexylsulphonyl.

In the context of the above-described substituted pyridines, sulphamoyl (aminosulphonyl) stands for the group --SO2 --NH2.

In the context of the above-described substituted pyridines, aryl in general stands for an aromatic radical having 6 to about 12 carbon atoms. Preferred aryl radicals are phenyl, naphthyl and biphenyl.

In the context of the above-described substituted pyridines, aryloxy in general stands for an aromatic radical having 6 to about 12 carbon atoms which is bonded via an oxygen atom. Preferred aryloxy radicals are phenoxy and naphthyloxy.

In the context of the above-described substituted pyridines, arylthio in general stands for an aromatic radical having 6 to about 12 carbon atoms which is bonded via a sulphur atom. Preferred arylthio radicals are phenylthio and naphthylthio.

In the context of the above-described substituted pyridines, arylsulphonyl in general stands for an aromatic radical having 6 to about 12 carbon atoms which is bonded via an SO2 group. Examples which may be mentioned are phenylsulphonyl, naphthylsulphonyl and biphenylsulphonyl.

In the context of the above-described substituted pyridines, aralkyl in general stands for an aryl radical having 7 to 14 carbon atoms which s bonded via an alkylene chain. Aralkyl radicals having 1 to 6 carbon atoms in the aliphatic moiety and 6 to 12 carbon atoms in the aromatic moiety are preferred. Examples which maybe mentioned are the following alkyl radicals: benzyl, naphthylmethyl, phenethyl and phenylpropyl.

Aralkoxy in general stands for an aralkyl radical having 7 to 14 carbon atoms, the alkylene chain being bonded via an oxygen atom. Aralkoxy radicals having 1 to 6 carbon atoms in

the aliphatic moiety and 6 to 12 carbon atoms in the aromatic moiety are preferred. Examples which may be mentioned are the following aralkoxy radicals: benzyloxy, naphthylmethoxy, phenethoxy and phenylpropoxy.

In the context of the above-described substituted pyridines, aralkylthio in general stands for an aralkyl radical having 7 to about 14 carbon atoms, the alkyl chain being bonded via a sulphur atom. Aralkylthio radicals having 1 to 6 carbon atoms in the aliphatic moiety and 6 to 12 carbon atoms in the aromatic moiety are preferred. Examples which may be mentioned are the following aralkylthio radicals: benzylthio, naphthylmethylthio, phenethylthio and phenylpropylthio.

In the context of the above-described substituted pyridines, aralkylsulphonyl in general stands for an aralkyl radical having 7 to about 14 carbon atoms, the alkyl radical being bonded via an SO2 link. Aralkylsulphonyl radicals having 1 to 6 carbon atoms in the aliphatic moiety and 6 to 12 carbon atoms in the aromatic moiety are preferred. Examples which may be mentioned are the following aralkylsulphonyl radicals: benzylsulphonyl, naphthylmethylsulphonyl, phenethylsulphonyl and phenylpropylsulphonyl.

In the context of the above-described substituted pyridines, alkoxycarbonyl can be represented, for example, by the formula CO-O-alkyl. In this connection, alkyl stands for a straight-chain or branched hydrocarbon radical having 1 to 12 carbon atoms. Lower alkoxycarbonyl having 1 to about 6 carbon atoms in the alkyl moiety is preferred. An alkoxycarbonyl having 1 to 4 carbon atoms in the alkyl moiety is particularly preferred. Examples which may be mentioned are the following alkoxycarbonyl radicals: methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl and isobutoxycarbonyl.

In the context of the above-described substituted pyridines, acyl in general stands for phenyl or straight-chain or branched lower alkyl having 1 to about 6 carbon atoms which are bonded via a carbonyl group. Phenyl and alkyl radicals having up to 4 carbon atoms are preferred. Examples which may be mentioned are benzoyl, acetyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl, butylcarbonyl and isobutylcarbonyl.

Halogen in general stands for fluorine, chlorine, bromine or iodine, preferably for fluorine, chlorine or bromine. Particularly preferably, halogen stands for fluorine or chlorine.

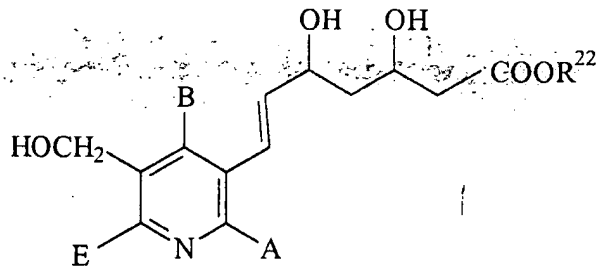
In the context of the above-described substituted pyridines, heteroaryl in general stands for a 5- to 6-membered aromatic ring which can contain oxygen, sulphur and/or nitrogen as hetero atoms and onto which can be fused further aromatic rings. 5- and 6-membered aromatic rings which contain one oxygen, one sulphur and/or up to 2 nitrogen atoms and which are optionally fused to benzene are preferred. Heteroaryl radicals which may be mentioned as particularly preferred are thienyl, furyl, pyrolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, quinazolyl, quinoxalyl, phthalazinyl,

cinnolyl, thiazolyl, benzothiazolyl, isothiazolyl, oxazolyl, benzoxazolyl, isoxazolyl, imidazolyl, benzimidazolyl, pyrazolyl, indolyl and isoindolyl.

If R22 stands for an ester radical, then a physiologically tolerable ester radical is preferably meant by this, which is easily hydrolyzed in vivo to a freecarboxyl group and a corresponding physiologically tolerable alcohol. These include, for example, alkyl esters (C1 to C4) and aralkyl esters (C7 to C10), preferably lower alkyl esters and benzyl esters. Moreover, the following ester radicals may be mentioned: methyl esters, ethylesters, propyl esters and benzyl esters.

In the context of the above-described substituted pyridines, if R^{22} stands for a cation then a physiologically tolerable metal cation or ammonium cation is preferably meant. In this connection, alkali metalcations or alkaline earth metal cations such as, for example, sodium cations, potassium cations, magnesium cations or calcium cations, and alsoaluminum cations or ammonium cations, and also non-toxic substituted ammonium cations from amines such as dilower alkylamines, triloweralkylamines, procain, dibenzylamine, N,N'-dibenzylethylenediamine, N-benzyl-.beta.-phenylethylamine, N-methylmorpholine or N-ethylmorpholine, 1-ephenamine, dihydroabietylamine, N,N'-bis-dihydroabietylethylenediamine, N-lower alkylpiperidine and other amines which can be used for theformation of salts are preferred.

The antiviral statin or statin-like compounds disclosed in U.S. Patent Nos. 5,401,746, 5,169,857, and 5,006,530 also include substituted pyridines having the following, more specific, general structure:



wherein A represents phenyl or phenyl which is monosubstituted or disubstituted by a substituent selected from the group consisting of methyl, hydroxymethyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, methoxy, ethoxy, propoxy, isopropoxy, phenoxy, benzyloxy, fluorine, chlorine or trifluoromethyl;

B represents cyclopropyl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, or tert.-butyl;

E represents methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, pentyl, isopentyl, hexyl or isohexyl; and

R^{22} represents hydrogen, lower alkyl, phenyl, benzyl or a physiologically tolerable metal or ammonium cation. These compounds may be synthesized or isolated from natural sources according to methods and techniques well known in the art.

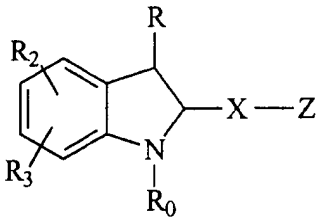
The compounds disclosed in U.S. Patent No. 5,273,995 include the following: [R-(R*,R*)]-2-(4-fluorophenyl)-.beta.,.delta.-dihydroxy-5-((1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, pharmaceutically acceptable salts and pro-drug esters thereof; and

(2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahy dro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (including the lactone form of the heptanoic acid); and

[R-(R*,R*)]-2-(4-fluorophenyl)-.beta.,.delta.-dihydroxy-5-(1-methylethyl)- 3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, its pharmaceutically acceptable salts and/or pro-drug esters or (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide acid; and

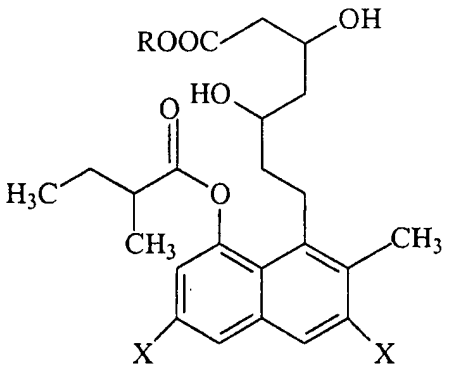
closely related structural analogs having anti-viral activity. These compounds may be synthesized or isolated from natural sources according to methods and techniques well known in the art.

The anti-viral statin or statin-like compounds disclosed in U.S. Patent No. 4,739,073 include compounds having the following structure:



wherein one of R and R_0 is an unsubstituted, mono-substituted, bi-substituted, or tri-substituted aromatic ring, preferably a benzyl ring and the other is primary or secondary C_{1-6} alkyl not containing an asymmetric carbon atom, C_{3-6} cycloalkyl or phenyl$(CH_2)_m$ --. These compounds may be synthesized or isolated from natural sources according to methods and techniques well known in the art.

The anti-viral statin or statin-like compounds disclosed in U.S. Patent Nos. 4,448,979 and 4,346,227 include compounds having the following general structure wherein:



wherein R represents a hydrogen atom or a C1 -C5 alkyl group and one of the two X's represents a hydroxyl group and the other represents, preferably, a hydrogen or a C1-C5 alkyl, and pharmaceutically acceptable salts and pro-drug esters thereof and the corresponding lactone in which the R_1 moiety is lost It is noted that, in view of the number of asymmetric carbon atoms in these compounds, a variety of geometric isomers are possible.

Methods of administration and formulations. With regard to the types of formulations in which the active compounds according to the present invention can be administered, as well as any additives to be included with the active compounds in the formulations, and the possible routes of administration, it is well known to those of skill in the art that such formulations can be provided in a wide variety of types, and it is within the skill or ordinary artisans to select a specific formulation and route of administration and then test suitability for use or in use. Furthermore, suitable formulations and routes of administration can be determined by further taking into account relevant disclosure known in the art (e.g., with regard to use of mevastatin, lovastatin, pravastatin and simvastatin, by reference to any of the large amount of information known in the art concerning formulations of the particular compound or compounds for administering to patients; with regard to use of one or more compound disclosed in any of U.S. Patents Nos. 4,346,227, 4,448,979, 4,739,073, 5,273,995, 5,169,857, 5,006,530, and 5,401,746, by reference to the particular patent or patents in which the compound is described or encompassed, in particular, to disclosure in the patent or patents which relates to formulations or routes of administration). The entireties of U.S. Patents Nos. 4,346,227, 4,448,979, 4,739,073, 5,273,995, 5,169,857,

5,006,530, and 5,401,746 are hereby incorporated here by reference for each of their disclosures relating to formulations and routes of administration.

With regard to dosage and duration of treatment, it is recognized that the ability of an artisan skilled in pharmaceutical administration of drugs to determine suitable dosages depending on many inter-related factors is well-known, and skilled artisans are readily able to monitor patients to determine whether treatment should be started, continued, discontinued or resumed at any given time. For example, dosages of the compounds are suitably determined depending on the Individual cases taking symptoms, age and sex of the subject and the like into consideration. The amount of a compound to be incorporated into the pharmaceutical composition of the invention varies with the dosage form, solubility and chemical properties of the compound, administration route, administration scheme and the like. An effective amount for a particular patient may vary depending on factors such as the condition being treated, the overall health of the patient, the method route and dose of administration and the severity of side effects. Dosages should be varied according to side effects (if any) and blood cell counts which should be monitored frequently, preferably every several days. Determination of the appropriate dose is made by the clinician using parameters known in the art. Generally, the dose begins with an amount somewhat less than the optimum dose and it is increased by small increments thereafter until the desired or optimum effect is achieved. Suitable dosages can be determined by further taking into account relevant disclosure known in the art (e.g., with regard to use of mevastatin, lovastatin, pravastatin and simvastatin, by reference to any of the large amount of information known in the art concerning administration of the particular compound or compounds to patients; with regard to use of one or more compound disclosed in any of U.S. Patents Nos. 4,346,227, 4,448,979, 4,739,073, 5,273,995, 5,169,857, 5,006,530, and 5,401,746, by reference to the particular patent or patents in which the compound is described or encompassed, in particular, to disclosure in the patent or patents which relates to dosage and duration of treatment, as well as other factors involved in medical treatments of patients (including humans and animals). The entireties of U.S. Patents Nos. 4,346,227, 4,448,979, 4,739,073, 5,273,995, 5,169,857, 5,006,530, and 5,401,746 are incorporated here by reference for each of their disclosures relating to dosage, duration of treatment and other factors involved in medical treatments.

The compounds for use in accordance with the present invention can be obtained readily by those skilled in the art. In addition, compounds can be obtained in accordance with relevant disclosure known in the art (e.g., with regard to mevastatin, lovastatin, pravastatin and simvastatin. by reference to any of the large amount of information known in the art concerning methods of obtaining the particular compound or compounds; with regard to one or more compound disclosed in any of U.S. Patents Nos. 4,346,227,

4,448,979, 4,739,073, 5,273,995, 5,169,857, 5,006,530, and 5,401,746, by reference to the particular patent or patents in which the compound is described or encompassed, in particular, to disclosure in the patent or patents which relates to methods of obtaining the compounds. The entireties of U.S. Patents Nos. 4,346,227, 4,448,979, 4,739,073, 5,273,995, 5,169,857, 5,006,530, and 5,401,746 are incorporated here by reference for each of their disclosures. relating to obtaining the compounds used for treatment.

The compounds disclosed herein as having antiviral properties may be administered alone or in combination with one or more other anti-viral drug, and/or one or more other drug administered to counteract any condition caused by one or more viral infection and/or by a therapy given to combat one or more viral infection. Such drugs, e.g., AZT, ribavirin, etc., are well known to those of skill in the art.

The components of any of the combination therapies disclosed herein can be administered simultaneously (in a combination formulation), essentially simultaneously (e.g., administration of each compound a few minutes or a few hours apart), or can be administered sequentially, e.g., several days apart, or more than a week apart. For example, according to the present invention, a compound according to the invention and a second anti-viral agent can be administered together, or essentially simultaneously, e.g., administration of each compound a few minutes or a few hours apart, or can be administered sequentially, e.g., several days apart, or more than a week apart. All such variations in administration of the combination therapy are encompassed within the scope of the invention.

As a general proposition, a dosage in the range of from about 0.1 to about 50 mg/kg/day will have therapeutic, anti-viral efficacy within the meaning of the present invention. Typically, a dosage in the range of from about 0.5 mg/kg/day to about 10 mg/kg/day will be employed. A daily dosage of a statin compound will typically comprise about 10 to about 1000 mg, usually about 20 to about 500 mg, which may be administered as a single dose or as two or more subdoses. Such doses or subdoses may be administered at one or more sites or by one or more than one route of administration. The duration for the treatment is usually once per day for a sufficient length of time, typically about 1-4 weeks, for the patient to become asymptomatic, or for one or more symptoms to abate noticeably.

In accordance with a preferred mode of using the present invention, a compound of the present invention may be administered orally, topically in creams, aerosol for nasal inhibition of, for example, Rhinovirus infections, intramuscularly (IM), intravenously (IV), or subcutaneously (SC). Preferred embodiments include IV administration using a statin compound that is micronized to an average particle diameter of about 0.1-10 μM, generally about 0.5-5 μM. In some embodiments, a statin such as mevastatin or lovastatin is

micronized to a size of about 5 μM or less and the micronized compound is suspended in sterile saline or buffer, which is administered by an IV route. Compounds of the invention and their pharmaceutically or physiologically, acceptable salts, are thus administered by any route suitable to the condition to be treated, including oral, rectal, nasal, topical (including ocular, buccal or sublingual), vaginal, parenteral (including subcutaneous, intramuscular, intravenous, intraperitoneal, intradermal, intrathecal, intradural and epidural) and pulmonary by aerosol.

Suitable formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques, excipients and formulations generally are found in, e.g., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, PA 1985, 17th edition, which is incorporated herein by reference. Methods to make formulations suitable for use in the present invention include the step of bringing into association a statin compound with one or more excipients or carriers. In general, such formulations are prepared by uniformly and intimately bringing into association a statin compound with liquid excipients or finely divided solid excipients or both, and then, if appropriate, shaping the product.

Formulations suitable for oral administration in the present invention may be presented as discrete units such as capsules, cachets or tablets, each containing a predetermined amount of statin compound; as a powder or granules; as solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The statin compound may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more excipients. Compressed tablets may be prepared by compressing in a suitable machine the statin compound in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the statin compound therein.

Formulations suitable for buccal administration include lozenges comprising a statin compound in a flavored basis, usually sucrose and acacia or tragacanth.

Formulations suitable for parenteral administration are usually sterile and include aqueous and non-aqueous injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-

dose or multi-dose containers, for example sealed ampoules and vials with elastomeric stoppers, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described. Unit dosage formulations will typically contain a daily dose or unit daily sub-dose, as recited above, or an appropriate fraction thereof.

To the extent not already indicated, it will be understood by those of ordinary skill in the art that any one of the various specific embodiments herein described and illustrated may be further modified to incorporate features shown in any of the other embodiments disclosed herein.

Therapeutic applications. For therapeutic applications, the compositions disclosed herein will typically comprise one or more anti-viral statin or statin-like compounds, and, the methods disclosed herein will utilize such compositions, which will contain one, two or more of such compounds, usually one. While it is possible for the compounds of the invention to be administered as pure compounds it is preferable to present them as pharmaceutical formulations. The formulations of the present invention comprise at least one statin compound together with one or more acceptable carriers or excipients and optionally other therapeutic agents, e.g., α–IFN, ribavirin, a nucleoside analog or a protease inhibitor. The one or more carriers or excipients must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the patient.

The compounds of this invention are useful in the treatment or prophylaxis of one or more flaviviral or togaviral infections in man or animals. Togavirus and flavivirus infections that can be treated with statin compounds include human hepatitis C virus (HCV), California encephalitis virus, St. Louis encephalitis virus, western equine encephalitis virus, eastern equine encephalitis virus, Colorado tick fever virus, LaCrosse encephalitis virus, Japanese encephalitis virus, yellow fever virus, Venezuelan equine encephalitis virus, Murray valley fever virus, tick-borne encephalitis viruses, GB virus A, GB virus B, GB virus C, Dengue virus 1, Dengue virus 2, Dengue virus 3, Dengue virus 4, Semliki Forest virus and Sindbis virus. The rubiviruses include human rubella virus. Pestiviruses include mucosal disease viruses such as bovine virus diarrhea virus, hog cholera virus and sheep border disease virus.

In addition to preventing or treating togaviral infections, the statin compounds can be used to treat vertebrate subjects (humans, animals or mammals) who are coinfected with a togavirus and another virus, such as a retrovirus or a second togavirus. Retroviruses such as a human immunodeficiency virus, e.g., HIV1 or HIV2, a simian

immunodeficiency virus, a recombinant human-simian immunodeficiency virus (e.g., $SHIV_{229}$), a feline immunodeficiency virus or a feline or murine leukemia or sarcoma virus can be treated as described herein. Coinfections with hepatitis viruses may be treated using the compounds of the invention, e.g., a HCV and HIV coinfection. In these embodiments, the subject will typically be one who has been tested to determine that (i) one or more togavirus infections is present (HCV, etc.) and (ii) a second virus infection is present, e.g., a RNA virus infection such as a retrovirus such as HIV1, HIV2, etc. or a papillomavirus infection, e.g., a human papillomavirus.

The methods disclosed herein are useful in the treatment of, or ameliorate one or more symptoms associated with, the conditions or infections disclosed herein. These compositions and formulations may also be used to treat, or ameliorate one or more symptoms associated with, a retroviral infection such as a HIV1 or HIV2 infection in humans. As used herein, phrases such as "amelioration of one or more symptoms associated with" means that such compounds or formulations may be used to reduce replication of an infectious agent or to reduce the number of infectious agents that are present in a subject or to ameliorate one or more symptoms associated with, or caused by, the condition or infection (e.g., reduced fever, a shortened duration or degree of pain, or a noticeable reduction of or elimination of diarrhea or fatigue).

In addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring or coloring agents.

The present invention further provides veterinary compositions comprising one or more anti-viral statin or statin-like compound together with a veterinary carrier therefor. Veterinary carriers are materials useful for the purpose of administering the composition to cats, dogs, horses, mice, rats, hamsters, rabbits and other animals and may be solid, liquid or gaseous materials that are otherwise inert or acceptable in the veterinary art and are compatible with a statin compound. These veterinary compositions may be administered orally, parenterally (e.g., IV) or by any other desired route, e.g., as described herein.

EXAMPLES

The tests described below demonstrate utility of the present invention by virtue of pharmacological activity of compositions of the present invention. These, tests are presented as illustrations of the use of the present invention, and should not be interpreted as in any way limiting the scope of the present invention. as it is defined in the claims.

In order to demonstrate the efficacy of the compounds according to the present invention in the treatment of viral infections. a number of tests were conducted, as reported below.

EXAMPLE 1

Example 1 was an in vitro test in which simvastatin was tested in MDBK cells against bovine virus diarrhea virus (BVDV). In view of the fact that no accepted model exists for HCV, new compounds for use in the treatment of HCV are tested for activity against BVDV, a virus which acts in a manner which is analogous to HCV The parameters of the test, and the test results are shown in Tables 1-1 through 1-3 (which may be graphed by depicting % of control cell viability and % reduction in viral CPE as a fuction of drug concentration), below:

Table 1-1

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plastic background					
A	0.335	0.335	0.358	0.369	0.395	0.560	0.000	0.000	0.003	0.004	0.002	0.007
		cc/vc					tox	drug MST 67 experimental			cc/vc	tox
B		1.422					1.784	0.212	0.215	0.237	1.568	0.670
C		1.294					1.320	0.236	0.211	0.261	1.328	1.610
D		1.221					1.493	0.398	0.597	0.795	1.404	1.915
E		0.202					1.684	0.540	0.534	0.546	0.574	1.740
F		0.185					1.656	1.642	1.717	1.778	0.578	1.758
G		0.193					1.272	1.431	1.328	1.448	0.312	0.968
							colorimetric background					
H							0.3 32	0.321	0.326	0.316	0.321	0.321

tox = cell toxicity cc = cell control vc = virus control BOLD = highest drug conc. values shown are optimal densities

Table 1-2

Reagent	0.392
Virus Control	-0.051
Cell Control	0.981
Differential	1.032

	25%	50%	95%
TC (μM)	> 20.00	> 20.00	> 20.00
IC (μM)	0.49	2.89	5.79
Antiviral Index (AI)	> 41.06	> 6.91	> 3.46

Table 1-3

Row on Plate		Conc. (μM)	Antiviral Test Values Mean O.D.	Antiviral Test Values % Red. In CPE	Cytotoxicity Test Values Mean O.D.	Cytotoxicity Test Values % Cell Viability	Colorimetric Control
low	B	0.0625	-.048	0%	0.906	92%	-.071
	C	0.2	-.034	0%	1.144	100%	-.071
	D	0.62	0.332	32%	1.388	100%	-.076
	E	2	0.265	26%	1.386	100%	-.066
	F	6.25	1.443	100%	1.385	100%	-.071
high	G	20	1.122	100%	0.788	80%	-.060

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EXAMPLE 2

Example 2 was a comparative in vitro test in which ribavirin was tested (as a standard) in MDBK cells against BVDV. The parameters of the test, and the test results are shown in Tables 2-1 through 2-3 (which may be graphed by depicting % of control cell viability and % reduction in viral CPE as a fuction of drug concentration), below:

Table 2-1

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plastic background					
A	0.703	0.377	0.372	0.413	0.438	0.569	0.015	0.014	0.014	0.015	0.015	0.013
		cc/vc					tox	drug MST 67 experimental			cc/vc	tox
B		1.082					1.121	0.253	0.262	0.269	1.327	0.908
C		0.930					1.120	0.247	0.171	0.208	0.969	0.967
D		1.124					1.109	0.448	0.393	0.308	1.132	1.025
E		0.195					1.090	0.288	0.334	0.943	0.201	0.961
F		0.265					0.824	0.687	0.774	0.714	0.213	0.763
G		0.230					0.525	0.514	0.528	0.523	0.241	0.558
							colorimetric background					
H							0.372	0.344	0.296	0.347	0.319	0.319

tox = cell toxicity cc = cell control vc = virus control BOLD = highest drug conc. values shown are optimal densities

Table 2-2

Reagent	0.479
Virus Control	-0.255
Cell Control	0.615
Differential	0.870

	25%	50%	95%
TC (μG/mL)	9.50	21.20	> 32.00
IC (μG/mL)	0.57	2.44	----
Antiviral Index (AI)	16.79	8.65	----

Table 2-3

Row on Plate		Conc. (μg/mL)	Antiviral Test Values Mean O.D.	Antiviral Test Values % Red. In CPE	Cytotoxicity Test Values Mean O.D.	Cytotoxicity Test Values % Cell Viability	Colorimetric Control
low	B	0.1	0.197	23%	0.696	100%	-.160
	C	0.32	0.145	17%	0.725	100%	-.160
	D	1	0.291	33%	0.720	100%	-.132
	E	3.2	0.481	55%	0.730	100%	-.183
	F	10	0.636	73%	0.450	73%	-.135
high	G	32	0.405	47%	0.170	28%	-.107

EXAMPLE 3

Example 3 was an in vitro test in which simvastatin was tested in MDBK cells against BVDV. The parameters of the test, and the test results are shown in Tables 3-1 through 3-3 (which may be graphed by depicting % of control cell viability and % reduction in viral CPE as a fuction of drug concentration), below:

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Table 3-1

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plastic background					
A	0.354	0.354	0.406	0.415	0.437	0.437	0.049	0.021	0.023	0.025	0.022	0.022
		cc/vc					tox	drug MST 67 experimental			cc/vc	tox
B		1.936					2.041	1.668	0.372	0.354	1.976	0.845
C		1.723					1.850	1.976	0.794	0.646	1.780	1.999
D		1.769					1.788	1.740	1.175	1.075	1.751	1.922
E		0.194					0.292	0.274	0.249	0.250	0.284	0.363
F		0.212					0.194	0.216	0.215	0.213	0.281	0.378
G		0.247					0.206	0.226	0.229	0.228	0.222	0.416
							colorimetric background					
H							0.389	0.403	0.382	0.382	0.349	0.349

tox = cell toxicity cc = cell control vc = virus control BOLD = highest drug conc.
values shown are optimal densities

Table 3-2

Reagent	0.401
Virus Control	-0.161
Cell Control	1.422
Differential	1.582

		25%	50%	95%
TC (μG/mL)		9.69	13.10	19.30
IC (μG/mL)	<	0.63	1.15	----
Antiviral Index (AI)	>	15.50	11.42	----

Table 3-3

Row on Plate		Conc. (μg/mL)	Antiviral Test Values Mean O.D.	Antiviral Test Values % Red. In CPE	Cytotoxicity Test Values Mean O.D.	Cytotoxicity Test Values % Cell Viability	Colorimetric Control
low	B	0.625	0.610	39%	1.095	77%	-.052
	C	2	0.951	60%	1.576	100%	-.052
	D	6.2	1.108	70%	1.473	100%	-.018
	E	20	0.036	2%	-.055	0%	-.018
	F	62.5	-.028	0%	-.117	0%	0.003
high	G	200	-.002	0%	-.079	0%	-.011

EXAMPLE 4

Example 4 was an in vitro test in which pravastatin was tested in MDBK cells against BVDV. The parameters of the test, and the test results are shown in Tables 4-1 through 4-3 (which may be graphed by depicting % of control cell viability and % reduction in viral CPE as a fuction of drug concentration), below:

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Table 4-1

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent backgroun						plastic background					
A	0.426	0.406	0.418	0.420	0.443	0.546	0.022	0.022	0.022	0.023	0.022	0.021
	tox	cc/vc	drug MST 67 experimental			tox					cc/vc	
B	1.950	1.950	0.734	1.226	0.234	1.789					2.107	
C	1.970	1.870	0.349	0.208	0.227	1.751					1.759	
D	2.091	1.858	0.759	0.185	0.979	1.805					1.804	
E	2.120	0.219	0.305	0.292	0.280	1.866					0.203	
F	2.051	0.230	0.367	0.240	0.278	1.865					0.273	
G	1.973	0.244	0.467	0.370	0.659	1.958					0.238	
	colorimetric background											
H	0.448	0.448	0.461	0.470	0.456	0.459						

tox = cell toxicity cc = cell control vc = virus control BOLD = highest drug conc.
values shown are optimal densities

Table 4-2

Reagent	0.443
Virus Control	-0.209
Cell Control	1.448
Differential	1.657

	25%	50%	95%
TC (μM)	> 200.00	> 200.00	> 200.00
IC (μM)	< 0.63	----	----
Antiviral Index (AI)	> 320.00	----	----

Table 4-3

Row on Plate		Conc. (μM)	Antiviral Test Values Mean O.D.	% Red. In CPE	Cytotoxicity Test Values Mean O.D.	% Cell Viability	Colorimetric Control
low	B	0.625	0.481	29%	1.410	97%	0.016
	C	2	0.014	1%	1.404	97%	0.013
	D	6.25	0.380	23%	1.478	100%	0.027
	E	20	0.040	2%	1.532	100%	0.018
	F	62.5	0.055	3%	1.510	100%	0.005
high	G	200	0.259	16%	1.517	100%	0.005

EXAMPLE 5

Example 5 was an in vitro test in which lovastatin was tested in MDBK cells against BVDV. The parameters of the test, and the test results are shown in Tables 5-1 through 5-3 (which may be graphed by depicting % of control cell viability and % reduction in viral CPE as a fuction of drug concentration), below:

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Table 5-1

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plastic background					
A	0.426	0.406	0.418	0.420	0.443	0.546	0.022	0.022	0.022	0.023	0.022	0.021
		cc/vc					tox	drug VTN 22 experimental			cc/vc	tox
B		1.950					2.029	0.278	0.545	0.418	2.107	0.973
C		1.870					1.853	0.393	0.505	0.616	1.759	2.141
D		1.858					1.944	0.421	0.447	0.744	1.804	2.345
E		0.219					1.966	1.998	1.415	1.975	0.203	2.055
F		0.230					1.612	1.642	1.696	1.773	0.273	1.640
G		0.244					0.210	0.220	0.218	0.218	0.238	0.356
							colorimetric background					
H							0.435	0.432	0.428	0.429	0.391	0.391

tox = cell toxicity cc = cell control vc = virus control BOLD = highest drug conc.
values shown are optimal densities

Table 5-2

Reagent	0.443
Virus Control	-0.209
Cell Control	1.448
Differential	1.657

	25%	50%	95%
TC (μM)	74.20	116.00	192.00
IC (μM)	6.85	10.00	20.00
Antiviral Index (AI)	10.84	11.56	9.58

Table 5-3

Row on Plate		Conc. (μM)	Antiviral Test Values Mean O.D.	Antiviral Test Values % Red. In CPE	Cytotoxicity Test Values Mean O.D.	Cytotoxicity Test Values % Cell Viability	Colorimetric Control
low	B	0.625	0.231	14%	1.110	77%	-.052
	C	2	0.322	19%	1.606	100%	-.052
	D	6.2	0.317	19%	1.715	100%	-.014
	E	20	1.577	95%	1.582	100%	-.015
	F	62.5	1.480	89%	1.194	82%	-.011
high	G	200	-.008	0%	-.152	0%	-.008

EXAMPLE 6

Example 6 was a test in which mevastatin was tested in PBMCs against the ROJO strain of the HIV virus. The parameters of the test, and the test results are shown in Table 6 (which may be graphed by depicting % of virus control and % of cell control as a function of concentration), revealing an IC_{50} = 0.3145 μM and a TC_{50} = 2.658716 μM (TI = 8.4531), below:

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Table 6

RT ACTIVITY (cpm)

CONC (μM)	200	64	20.48	6.554	2.097	0.671	0.215	0.069	0.022	0
SAMPLE 1	52.2	88.3	64.3	152.6	224.9	3430.5	6617.5	12348.0	10518.0	13361.0
SAMPLE 2	72.3	84.3	108.4	76.3	241.0	2108.6	10401.2	8334.3	8985.5	13361.0
SAMPLE 3	40.2	96.4	76.4	104.4	116.5	2016.3	6517.1	14460.7	14239.5	13361.0
MEAN	54.9	89.7	83.0	111.1	194.1	2518.5	7845.3	11714.3	11247.7	13361.0
% VC	0.4	0.7	0.6	0.8	1.5	18.8	58.7	87.7	84.2	100.0

TOXICITY VALUES (XTT-O.D. @ 450/650 nm)

CONC (μM)	200	64	20.48	6.554	2.097	0.671	0.215	0.069	0.022	0
SAMPLE 1	.0189	0.191	0.261	0.349	0.569	1.130	1.289	1.676	1.734	1.284
SAMPLE 2	0.165	0.188	0.255	0.420	0.727	0.954	1.196	1.397	1.358	1.284
SAMPLE 3	0.163	0.178	0.234	0.401	0.739	1.037	1.173	1.247	1.398	1.284
MEAN	0.172	0.186	0.250	0.390	0678	1.040	1.219	1.440	1.497	1.284
% CC_s	13.4	14.5	19.5	30.4	52.8	81.0	95.0	112.1	116.6	100.0

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EXAMPLE 7

Example 7 was a comparative test in which AZT (as a standard) was tested in PBMCs against ROJO. The parameters of the test, and the test results are shown in Table 7 (which may be graphed by depicting % of virus control and % of cell control as a function of concentration), revealing an IC_{50} = 0.0082 μM and a TC_{50} > 4 μM (TI > 487), below:

Table 7

RT ACTIVITY (cpm)

CONC (μM)	4	1.28	0.4096	0.131	0.042	0.013	0.0043	0.0014	0.0004	0
SAMPLE 1	52.2	100.4	176.7	56.2	60.2	1526.2	14948.0	8804.7	6866.6	13361.0
SAMPLE 2	56.2	80.3	92.4	1554.3	5295.1	345.5	514.1	14509.2	12509.7	13361.0
SAMPLE 3	76.3	72.3	72.3	216.9	120.5	2080.6	16458.0	13264.5	26442.6	13361.0
MEAN	61.6	84.3	113.8	609.1	1825.3	1317.4	10640.0	12192.8	15273.0	13361.0
% VC	0.5	0.6	0.9	4.6	13.7	9.9	79.6	91.3	114.3	100.0

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TOXICITY VALUES (XTT-O.D. @ 450/650 nm)

CONC (μM)	4	1.28	0.4096	0.131	0.042	0.013	0.0043	0.0014	0.0004	0
SAMPLE 1	0.785	1.085	1.369	1.220	1.139	1.237	1.076	1.044	1.162	1.284
SAMPLE 2	1.273	1.031	1.077	1.269	1.029	1.112	1.235	1.236	1.159	1.284
SAMPLE 3	1.200	1.198	1.286	1.042	1.488	1.227	1.521	1.573	1.293	1.284
MEAN	1.086	1.105	1.244	1.177	1.219	1.192	1.277	1.284	1.205	1.284
% CC	84.6	86.0	96.9	91.7	94.9	92.8	99.5	100.0	93.8	100.0

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EXAMPLE 8

Example 8 was a comparative test in which AZT was tested in macrophages against the Ba-L strain of the HIV virus. The parameters of the test, and the test results are shown in Table 8 (which may be graphed by depicting % of virus control and % of cell control as a function of concentration), revealing an IC_{50} = 0.0085 μM and a TC_{50} > 4 μM (TI > 471), below:

Table 8

p24 ACTIVITY (pg/ml)

CONC (μM)	4	1.28	0.41	0.13	0.042	0.013	0.0043	0.0014	0.0004	0
SAMPLE 1	0.0	0.0	0.0	0.0	175.3	281.5	262.6	548.0	541.3	640.3
SAMPLE 2	0.0	0.0	0.0	0.0	99.6	186.8	460.1	765.2	732.0	640.3
SAMPLE 3	0.0	0.0	0.0	0.0	27.9	104.3	573.7	366.1	679.0	640.3
MEAN	0.0	0.0	0.0	0.0	100.9	190.9	432.1	559.8	650.8	640.3
% VC	0.0	0.0	0.0	0.0	15.8	29.8	67.5	87.4	101.6	100.0

TOXICITY VALUES (XTT-O.D. @ 450/650 nm)

CONC (μM)	4	1.28	0.41	0.13	0.042	0.013	0.0043	0.0014	0.0004	0
SAMPLE 1	1.481	1.855	1.519	1.127	1.512	1.073	1.223	1.231	1.433	1.327
SAMPLE 2	1.505	1.408	1.464	1.050	1.245	1.412	1.559	1.409	1.387	1.327
SAMPLE 3	1.505	1.252	1.243	1.412	1.474	1.319	1.110	1.036	1.431	1.327
MEAN	1.497	1.050	1.409	1.196	1.410	1.268	1.297	1.225	1.417	1.327
% CC	112.8	113.4	106.2	90.2	106.3	95.6	97.8	92.3	106.8	100.0

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EXAMPLE 9

Example 9 was a test in which mevastatin was tested in macrophages against Ba-L. The parameters of the test, and the test results are shown in Table 9 (which may be graphed by depicting % of virus control and % of cell control as a function of concentration), revealing an IC_{50} = 12.9528 μM and a TC_{50} > 400 μM (TI > 31) , below.

Table 9

p24 ACTIVITY (pg/ml)

CONC (μM)	400	128	40.96	13.11	4.19	1.34	0.43	0.14	0.04	0
SAMPLE 1	55.6	83.4	118.5	328.9	701.6	583.6	636.7	598.8	635.3	640.3
SAMPLE 2	29.9	33.3	80.7	157.8	247.0	514.9	541.3	553.5	612.3	640.3
SAMPLE 3	85.4	90.8	301.8	463.5	593.4	615.0	667.8	667.8	713.8	640.3
MEAN	57.0	69.2	167.0	316.7	514.0	571.2	615.3	606.7	653.8	640.3
% VC	8.9	10.8	26.1	49.5	80.3	89.2	96.1	94.8	102.1	100.0

TOXICITY VALUES (XTT-O.D. @ 450/650 nm)

CONC (μM)	400	128	40.96	13.11	4.19	1.34	0.43	0.14	0.04	0
SAMPLE 1	1.430	1.403	1.787	1.525	1.254	1.349	1.620	1.557	1.875	1.327
SAMPLE 2	1.205	1.216	1.449	1.320	1.259	1.362	1.588	1.361	1.097	1.327
SAMPLE 3	0.895	1.225	1.179	1.319	1.413	1.232	1.436	1.362	1.215	1.327
MEAN	1.177	1.281	1.472	1.388	1.309	1.314	1.548	1.427	1.396	1.327
% CC	88.7	96.6	110.9	104.6	98.6	99.0	116.7	107.5	105.2	100.0

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EXAMPLE 10

Example 10 was a test in which pravastatin was tested in macrophages against Ba-L. The parameters of the test, and the test results are shown in Table 10 (which may be graphed by depicting % of virus control and % of cell control as a function of concentration), revealing an IC_{50} = 34.25 μM and a TC_{50} = 189.53 μM (TI > 5.54). below:

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Table 10

pg/ml ACTIVITY

CONC (μM)	200	64	20	6.4	2	0.64	0.2	0.044	0.02	0
SAMPLE 1	177.6	199.4	487.4	449.4	488.5	347.8	352.0	338.8	505.3	552.4
SAMPLE 2	381.0	161.5	266.4	246.2	308.2	289.0	638.4	418.9	618.3	552.4
SAMPLE 3	148.5	82.4	279.3	377.0	319.7	918.8	442.2	634.1	398.8	552.4
MEAN	235.7	147.8	337.7	357.5	371.5	518.5	476.9	463.2	507.5	552.4
% VC	42.7	28.7	61.1	64.7	67.2	93.9	86.3	83.9	91.9	100.0

TOXICITY VALUES (XTT-O.D. @ 450/650 nm)

CONC (μM)	200	64	20	6.4	2	0.64	0.2	0.064	0.02	0
SAMPLE 1	1.814	2.351	1.728	2.122	2.579	2.853	3.048	3.072	3.214	3.100
SAMPLE 2	1.619	1.529	2.313	1.637	1.892	1.839	2.919	3.292	3.184	3.100
SAMPLE 3	1.098	2.220	2.164	2.000	2.377	2.266	3.331	3.041	2.971	3.100
MEAN	1.510	2.033	2.088	1.920	2.283	2.319	3.099	3.136	3.123	3.100
% CC	48.7	65.6	65.7	61.9	73.8	74.8	100.0	101.1	100.7	100.0

VIRUS AND CELL CONTROLS ARE PLATE AVERAGES

EXAMPLE 11

Example 11 was a test in which lovastatin was tested in macropharge against the Ba-L strain of HIV. The parameters of the test, and the etst results are shown in Table 11 (which may be graphed by depicting % of virus control and % of cell control as a function of concentration), revealing an IC_{50} = 13.49 μM and a TC_{50} = 58.06 μM (TI = 4.3039) , below

Table 11

pg/mL ACTIVITY

CONC (μM)	200	64	20	6.4	2	0.64	0.2	0.064	0.02	0
SAMPLE 1	208.4	203.7	124.7	266.7	416.8	406.8	429.8	231.7	325.1	488.9
SAMPLE 2	149.2	157.8	353.1	305.6	212.3	236.7	413.8	413.5	497.0	488.9
SAMPLE 3	76.9	158.6	108.0	321.9	288.9	374.8	341.4	444.3	782.5	488.9
MEAN	144.8	173.4	195.3	298.1	305.3	340.1	395.0	363.2	534.9	489.9
% VC	29.6	35.5	39.9	61.0	62.5	69.6	80.8	74.3	109.4	100.0

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TOXICITY VALUES (XTT-O.D. @450/650 nm)

CONC (μM)	200	64	20	6.4	2	0.64	0.2	0.064	0.02	0
SAMPLE 1	0.648	1.139	1.684	2.470	2.341	2.290	1.326	1.295	2.680	2.547
SAMPLE 2	0.365	0.399	2.590	2.691	2.584	2.383	2.381	2.267	2.284	2.547
SAMPLE 3	1.552	1.836	2.407	2.432	2.459	2.147	2.800	2.526	2.427	2.547
MEAN	0.855	1.125	2.227	2.531	2.461	2.273	2.169	2.029	2.464	2.547
% CC	36.6	44.2	87.4	99.4	96.6	89.3	85.2	79.7	95.7	100.0

VIRUS AND CELL CONTROLS ARE PLATE AVERAGES

EXAMPLE 12

Example 12 was a test in which simvastatin was tested in macrophages against Ba-L. The parameters of the test, and the test results are shown in Table 12 (which may be graphed by depicting % of virus control and % of cell control as a function of concentration), revealing an IC_{50} = 51.39 μM and a TC_{50} > 200 μM (TI > 3.8918), below:

Table 12

pg/mL ACTIVITY

CONC (μM)	200	64	20	6.4	2	0.64	0.2	0.064	0.02	0
SAMPLE 1	139.1	154.5	129.7	186.6	319.1	256.7	234.6	229.6	480.5	368.9
SAMPLE 2	65.6	70.6	425.7	277.7	298.7	264.4	193.2	372.7	217.5	368.9
SAMPLE 3	173.3	173.9	382.0	344.5	189.9	254.5	454.0	446.3	411.9	368.9
MEAN	126.0	133.0	312.5	289.6	269.2	158.5	293.9	349.5	363.3	368.9
% VC	34.2	36.1	84.7	73.1	73.0	70.1	79.7	84.8	98.5	100.0

TOXICITY VALUES (XTT-O.D. @ 450/650 nm)

CONC (μM)	200	64	20	6.4	2	0.64	0.2	0.064	0.02	0
SAMPLE 1	1.348	1.766	1.795	1.715	1.808	2.404	1.880	2.610	2.570	2.859
SAMPLE 2	1.742	1.607	1.912	2.671	3.266	1.876	2.964	2.661	2.379	2.859
SAMPLE 3	1.823	2.168	2.311	2.722	2.164	2.311	2.781	2.630	3.016	2.859
MEAN	1.638	1.847	2.006	2.369	2.413	2.197	2.542	2.364	2.655	2.859
% CC	57.3	64.6	70.2	82.9	84.4	76.8	88.9	92.1	92.9	100.0

VIRUS AND CELL CONTROLS ARE PLATE AVERAGES

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EXAMPLE 13

Example 13 was a test in which tovastatin was tested in PBMC against ROJO, The parameters of the test, and the test results are shown in Table 13 (which may be graphed by depicting % of virus control and % of cell control as a function of concentration), revealing an IC_{50} = 114.60 μM and a TC_{50} = 172.69 μM (TI =1.5069)), below:

Table 13

RT ACTIVITY (epm)

CONC (μM)	200	64	20	6.4	2	0.64	0.2	0.064	0.02	0
SAMPLE 1	76.3	8140.9	4889.0	7606.1	8675.8	10372.9	7988.3	15458.9	10863.6	8065.8
SAMPLE 2	60.2	6951.0	8004.3	7594.1	12549.3	8241.5	6323.8	13865.2	975.9	8065.8
SAMPLE 3	38.1	4073.3	6657.7	6617.4	5817.5	5612.6	6521.1	11515.4	9822.0	8065.8
MEAN	57.5	6386.4	8517.0	7272.5	9014.2	8075.7	6943.7	13613.2	10130.3	8065.8
% VC	0.7	79.2	80.8	90.2	111.8	100.1	86.1	168.8	125.61	100.0

TOXICITY VALUES (XTT-O.D. @ 450/650 nm)

CONC (μM)	200	64	20	6.4	2	0.64	0.2	0.064	0.02	0
SAMPLE 1	0.503	2.018	1.834	1.804	1.707	1.776	1.683	1.733	1.613	1.622
SAMPLE 2	0.485	2.034	2.121	1.998	2.071	2.004	1.836	2.022	1.583	1.622
SAMPLE 3	0.517	2.075	2.277	2.104	2.017	1.995	1.853	1.847	1.779	1.622
MEAN	0.502	2.042	2.077	1.969	1.932	1.925	1.794	1.867	1.658	1.622
% CC	30.9	125.8	128.1	121.4	119.1	118.7	110.6	115.1	102.2	100.0

VIRUS AND CELL CONTROLS ARE PLATE AVERAGES

EXAMPLE 14

Example 14 was a test in which pravastatin was tested in PBMC against ROJO. The parameters of the test, and the test results are shown in Table 14 (which may be graphed by depicting % of virus control and % of cell control as a function of concentration), revealing an IC_{50} = 105.12 μM and a TC_{50} > 200 μM (TI > 1.9)), below:

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Table 14

RT ACTIVITY (epm)

CONC (μM)	200	64	20	6.4	2	0.64	0.2	0.064	0.02	0
SAMPLE 1	743.1	2153.1	7957.1	7056.5	9352.4	8733.2	9581.6	8077.4	10845.1	11336.5
SAMPLE 2	305.2	5508.5	10478.4	18065.2	14308.6	11520.0	16063.6	9579.0	19148.1	11336.5
SAMPLE 3	3820.3	14602.6	8089.1	7345.6	11073.3	14028.4	17114.0	13248.4	11986.2	11336.5
MEAN	1622.9	7421.4	8441.5	10822.4	11578.1	11426.5	14253.1	10299.6	13993.1	11336.5
% VC	14.3	65.5	78.0	95.5	102.1	100.8	125.7	90.9	123.4	100.0

TOXICITY VALUES (XTT-O.D. @450/650 nm)

CONC (μMs)	200	64	20	6.4	2	0.64	0.2	0.064	0.02	0
SAMPLE 1	1.466	2.133	2.112	2.000	2.028	1.982	1.827	1.822	1.763	1.479
SAMPLE 2	1.439	2.230	2.398	2.221	2.029	2.038	2.106	1.918	1.765	1.479
SAMPLE 3	1.469	1.866	2.059	1.995	1.656	1.823	1.895	1.753	1.765	1.479
MEAN	1.458	2.076	2.190	2.072	1.904	1.948	1.943	1.831	1.764	1.479
% CC	98.6	140.4	148.1	140.1	128.8	131.7	131.4	123.6	119.3	100.0

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EXAMPLE 15

Example 15 was a test in which simvastatin was tested in PBMC against ROJO. The parameters of the test, and the test results are shown in Table 15 (which may be graphed by depicting % of virus control and % of cell control as a function of concentration), revealing an IC_{50} = 0.3145 μM and a TC_{50} = 2.658716 μM (TI = 8.4538), below:

Table 15

RT ACTIVITY (epm)

CONC (μM)	200	64	20	6.4	2	0.64	0.2	0.064	0.02	0
SAMPLE 1	64.3	5869.7	6641.7	5632.7	4836.8	7288.7	7647.7	9005.6	8221.6	8065.8
SAMPLE 2	60.2	5327.1	4133.5	8623.4	6147.0	9604.7	10417.0	10015.0	8905.0	8065.8
SAMPLE 3	60.2	7662.5	8104.7	6474.6	7485.6	6207.2	9081.8	6110.8	5395.4	8065.8
MEAN	61.6	6286.4	6293.3	6910.2	6156.5	7693.5	9048.8	8377.1	7507.3	8065.8
% VC	0.8	77.9	78.0	85.7	76.3	95.4	112.2	103.9	93.1	100.0

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TOXICITY VALUES (XTT-O.D. @ 450/650 nm)

CONC (μM)	200	64	20	6.4	2	0.64	0.2	0.064	0.02	0
SAMPLE 1	0.511	2.154	2.024	2.019	1.639	1.944	1.823	1.857	1.645	1.622
SAMPLE 2	0.516	2.475	2.660	2.498	2.596	2.411	2.364	2.262	2.001	1.622
SAMPLE 3	0.476	1.747	1.910	1.675	1.546	1.510	1.511	1.452	1.463	1.622
MEAN	0.501	2.125	2.198	2.064	1.994	1.955	1.899	1.867	1.703	1.622
% CC	30.9	131.0	135.5	127.3	122.9	120.5	117.1	114.5	105.0	100.0

VIRUS AND CELL CONTROLS ARE PLATE AVERAGES

Each of the various patent documents cited herein is hereby incorporated by reference. in its entirety, herein, to the extent permissible by applicable law. rule, or regulation.

WHAT IS CLAIMED IS:

1. A method of treating a viral infection in a vertebrate in need of such treatment, comprising administering to said patient a viral infection treatment effective amount of at least one antiviral statin and statin-like compound.

2. A method of treating hepatitis C in a vertebrate in need of such treatment, comprising administering to said patient a hepatitis C treatment effective amount of at least one antiviral statin and statin-like compound.

3. A method of treating hepatitis in a vertebrate in need of such treatment, comprising administering to said patient a hepatitis treatment effective amount of at least one antiviral statin and statin-like compound.

4. A method of treating HIV in a vertebrate in need of such treatment, comprising administering to said patient an HIV treatment effective amount of at least one antiviral statin and statin-like compound.

5. The method of Claim 1, 2, 3 or 4 wherein the vertebrate is a mammal.

6. The method of Claim 1, 2, 3 or 4 wherein the vertebrate is a human.

7. The method of Claim 1, 2, 3 or 4 wherein the antiviral statin and statin-like compound is pravastatin.

8. The method of Claim 1, 2, 3 or 4 wherein the antiviral statin and statin-like compound is lovastatinstatin.

9. The method of Claim 1, 2, 3 or 4 wherein the antiviral statin and statin-like compound is simvastatin.

10. The method of Claim 1, 2, 3 or 4 wherein the antiviral statin and statin-like compound is mevastatin.

11. A composition comprising antiviral statin and statin-like compound and at least one other anti-viral compound.

12. Use of an antiviral statin and statin-like compound in the manufacture of a medicament for use in treatment of viral infection.

13. Use of an antiviral statin and statin-like compound in the manufacture of a medicament for use in treatment of hepatitis C.

14. Use of an antiviral statin and statin-like compound in the manufacture of a medicament for use in treatment of hepatitis.

15. Use of an antiviral statin and statin-like compound in the manufacture of a medicament for use in the treatment of HIV.

16. A method of treating a vertebrate cell line having a viral infection, comprising administering to said cell line a viral infection-treatment effective amount of at least one antiviral statin and statin-like compound.

17. The method of Claim 16, wherein the vertebrate cell line is a mammalian cell line.

18. The method of Claim 16, wherein the vertebrate cell line is a human cell line.

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(54) Title: USE OF STATINS FOR TREATING VIRAL INFECTIONS

(57) Abstract: The present invention relates to methods of treating a vertebrate, particularly a mammal and more particularly murine or human patient, suffering from one or more viral infections, or a cell line infected with one or more viral infections, said viral infections including but not limited to the infections of the following viruses: hepatitis C, HIV, hepatitis A, hepatitis B, hepatitis G, or hepatitis H, by administering to said patient infected with at least one of virus at least one statin or statin-like compound determined to have anti-viral activity according to the present invention, said anti-viral statin or statin-like compound being selected from the group consisting of: mevastatin, lovastatin, pravastatin, simvastatin, and the compounds disclosed in U.S. Patents Nos. 4,346,227, 4,448,979, 4,739,073, 5,273,995, 5,169,857, 5,006,530, and 5,401,746.

INTERNATIONAL SEARCH REPORT

Interna al Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/00 A61P31/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MAZIERE J C ET AL: "LOVASTATIN INHIBITS HIV-1 EXPRESSION IN H9 HUMAN T LYMPHOCYTES CULTURED IN CHOLESTEROL-POOR MEDIUM" BIOMEDICINE AND PHARMACOTHERAPY,ELSEVIER, PARIS,FR, vol. 48, no. 2, 1994, pages 63-67, XP000965739 the whole document	1-18
P,X	WO 99 58505 A (WARNER LAMBERT CO ;LEOPOLD JUDITH (US); NEWTON ROGER SCHOFIELD (US) 18 November 1999 (1999-11-18) abstract; claims	1-18

[ ] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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INTERNATIONAL SEARCH REPORT

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9958505 A	18-11-1999	AU 3979299 A	29-11-1999